retained after dialysis to remove molecules with molecular weights of less than 6000-8000 daltons with the proviso that the larger molecule is not *Staphylococcal enterotoxin B* (SEB) or *Staphylococcal enterotoxin C* (SEC) or other native toxin.

REMARKS

Claims 50-55 are pending in this application. Although claims 50-53 are stated as being withdrawn, applicants note that they have been considered and stand rejected under various grounds of rejection.

1. Amendments

As required by 37 C.F.R. §1.121, attached hereto is a marked-up version of the changes made to the claims by the current amendment with additions indicated by underlining and deletions by brackets. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Claim 50, and thus its dependent claims, have been amended to exclude SEB or SEC or other native toxins from their scope. Applicants respectfully submit that the exclusion of these toxins is supported throughout the specification. The toxins SEB and SEC are identified in the application as being known in the art and the specific 12 mer amino acid sequences which are contained in SEB and SEC are set forth in the specification. See, e.g., page 4, lines 12-13, where it is stated that "[t]he gene sequences and deduced amino acid sequences of at least six staphylococcal enterotoxins ... are known, i.e., SEA, SEB, SEC, SEE, SED and SHE." See also, Figure 3 of the specification, which sets forth the specific 12-mer sequences. See also, page 24, lines 18-19 wherein it is stated that "[t]he preferred peptides of the invention are those which exclude full length native toxin molecules." See also, page 24, lines 23-25 of the specification wherein it is stated that "[t]he most preferred peptides of the invention do not contain amino acid sequences in the sequence in which they are found in any particular native toxin molecule."

Claims 50-55 have also been amended to include the term "purified." Support for the use of this term may be found in the specification on page 27, lines 7-10, where the polymerized molecules are dialyzed to recover small molecular weight molecules.

Claims 50 and 55 have been amended to include the definition of SEB and SEC, *Staphylococcal enterotoxin* B and *Staphylococcal enterotoxin* C.

Claims 50-55 have been amended to include the term "non-toxic." Support for the use of this term may be found in the specification on page 1, lines 21-25, where the "peptides of the invention are useful to prevent, treat, or protect against the toxic effects of bacterial toxins, including most, if not all, of the staphylococcal and streptococcal pyrogenic toxins."

Applicants respectfully submit that the above-mentioned amendments do not constitute new matter and respectfully request entry thereof.

2. The Pending Claims

Prior to entry of this amendment, claims 50-55 were pending, claims 50-53 were withdrawn from consideration and claims 54 and 55, stood rejected. However, as mentioned above, claims 50-53 are stated as being withdrawn, although applicants note that they have been considered and rejected under various grounds of rejection.

3. The rejection under 35 U.S.C. §112

The Examiner has rejected claims 50-55 under 35 U.S.C. §112, first paragraph, as containing subject matter which was allegedly not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree with and traverse this rejection.

The instant specification provides support for , *inter alia*, SEQ ID NOs: 32-80. Applicants respectfully direct the Examiner's attention to page 23, lines 1-7 of the specification as support for the claims including SEQ ID NOs:32-80. The consensus sequence #1b (SEQ ID NO: 30) distinctly indicates which amino acids may be substituted for $X_1$, $X_2$, and $X_4$, and further provides the more preferred amino acids. $X_1$ is V or I, preferably V; $X_2$ is L, E, K, P, or N, preferably E or L; and $X_4$ is D, N, E, Q, or H, preferably E. Since there is a limited number of

possible amino acids, especially in light of the preferred amino acids for substituting $X_1$, $X_2$, and $X_4$, the description requirement is fulfilled. In particular, there is sufficient guidance that would reasonably lead one of ordinary skill in the art to select the amino acids from the preferred amino acids in order to result in the peptide sequences of SEQ ID NOs: 32-80. SEQ ID NOs: 32-80 represent the possible peptides derived from the consensus sequence #1b (SEQ ID NO: 30). $X_1$, $X_2$, and $X_4$ may be substituted by 2, 5, and 5 amino acids, respectively, resulting in 50 possible combinations (2 X 5 X 5 = 50).

The addition of SEQ ID NO:32-80 to claims 50-55 does not present new matter. Support for the individual combinations disclosed in SEQ ID NOs:32-80 are provided as described above on page 23, lines 1-7, where the preferred amino acids are provided and determining all possible combinations would not be unduly burdensome. In fact, the disclosure on page 23, lines 1-7 teaches and provides motivation for one of ordinary skill in the art to choose the particular combination of amino acids for $X_1$, $X_2$, and $X_4$ to result in the amino acid sequences of SEQ ID NOS: 32-80. The choices for $X_1$, $X_2$, and $X_4$ are not too numerous for one to be directed to the particular combinations. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

The Examiner further states that "there is no support for a peptide, either SEQ ID NO:3 or 34 which are retained after dialysis to remove molecules with molecular weights of less then [sic] 6000-8000 daltons with the proviso that the larger molecule is not SEB or SEC or other native toxin" (Office Action 3/1/02-page 3, lines 9-11). Applicants respectfully disagree with this statement.

Applicants direct the Examiner's attention to page 23, line 25 through page 24, line 7 and page 24, lines 18-25, where a specifically exemplified polymer peptide having SEQ ID NO: 3 is "at least 6000-8000 daltons...[where] [s]mall peptides and/or contaminants may be removed by dialysis or other methods available in the art" and "[t]he preferred peptides of the invention are those which exclude full length native toxin molecules...[and] [t]he most preferred peptides of the invention do not contain amino acid sequences in the sequences in which they are

found in any particular native toxin molecule." Furthermore, Example 1 under "Construction of Synthetic Peptides" of the instant specification clearly cites that:

> synthetic peptides #1 [SEQ ID NO: 3] and #2 are not native peptides, i.e., their sequences differ from those found in native toxins. Variations of these peptides have also been constructed in order to generate concatenated polymers of the peptides. These polymers were constructed by the addition of glycine and of additional cysteine residues to the amino- and/or carboxyl- termini of the initial 2 peptides, thus facilitating concatenation via disulfide bond formation (37, 38, 39). The polymerized molecules were then dialyzed to remove molecules with molecular weights less than 6000-8000 daltons. (page 43, lines 7-18)

On page 26, lines 10-14 of the instant specification, a "peptide of the invention" is defined as "any substituted analog or chemical derivative of a peptide derived from one or both of the two consensus regions described herein," and includes SEQ ID NOs: 3 and 34. Therefore, these references provide support for peptides retained after dialysis to remove molecules with molecular weights of less than 6000-8000 daltons with the proviso that the larger molecule is not SEB or SEC or other native toxin. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

The Examiner has rejected claim 55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. More particularly, the Examiner states that acronyms, such as SEB and SEC, must be spelled out when used for the first time in a chain of claims. Claims 50 and 55 have been amended to overcome this rejection as suggested by the Examiner. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

4. The rejection under 35 U.S.C. §101

The Examiner has rejected claims 50-55 under 35 U.S.C. 101 because the peptide is allegedly a product of nature and would be naturally produced. Applicants respectfully disagree with and traverse this rejection; however, in order to expedite prosecution of the

application, applicants have amended the claims as suggested by the Examiner. Applicants have, here and above, amended claims 50-55 to recite the term "purified." Applicants respectfully request reconsideration and withdrawal of this §101 rejection.

5. Double Patenting

The Examiner has rejected claims 50-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8 of U.S. Patent No. 6,075,119 ('119). Applicants respectfully disagree with this double patenting rejection. Applicants have amended the claims to reflect the deletion of SEQ ID NO:3. In view of applicants' amendments, the instant claims 50-55 having SEQ ID NOs:32-80 are therefore not obvious over the sequences claimed in the '119 patent. However, applicants agree to file a terminal disclaimer once these claims are in condition for allowance, but for the double patenting rejection.

6. Rejection(s) under 35 U.S.C. §§102(b)

The Examiner has rejected claims 50-55 under 35 U.S.C. §102(b) as being anticipated by Iandolo, J.J. (*Annu. Rev. Microbiol.* 43: 375, 1989). The Examiner states that the prior art and the claimed invention appear to be the same or an obvious or analogous variant of the peptides claimed because they appear to possess the same or similar functional characteristics. The Examiner states that, since the PTO does not have the facilities for examining and comparing applicants' peptide with the peptide of the prior art reference, the burden is upon applicants to show an unobvious distinction between the material structural and functional characteristics of the claimed peptide and the peptide of the prior art. (Office Action, 3/1/02, p. 6-7, paragraph 3). Applicants respectfully traverse the rejection.

Applicants note that the Examiner has found SEQ ID NO: 3 to be free of the prior art. Since applicants claim SEQ ID NO: 3 in U.S. Patent No. 6,075,119 to Bannan, et al., applicants delete the recitation of SEQ ID NO: 3 in pending claims. The remaining sequences, like SEQ ID NO: 3, are not disclosed by the prior art.

First, applicants remind the Examiner that in order to anticipate a claim, the reference must teach every element of the claim. In particular, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Additionally, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Claims 50-55 are not anticipated by the Iandolo reference because Iandolo does not describe any of the specific sequences claimed by applicants.

Second, Table 2 of Iandolo reports the sequence similarities of two conserved regions of primary structured pyrogenic toxin and enterotoxin **sequences, not peptides** (emphasis added):

| **Toxin** | **Sequence** | | | |
|---|---|---|---|---|
| | 106 | 119 | 147 | 163 |
| SEA | CMYGGVTLHDNN***RL*** | | KKNVTVQELDLQARYL | |
| SEB | CMYGGVTEHHGN***OL*** | | KKKVTAQELDYLTRHYL | |
| SEC1 | CMYGGITKHEGN***HF*** | | KKSVTAQELDIKARNFL | |
| SED | CTYGGVTPHEGN***KL*** | | KKNVTVQELDAQARRYL | |
| SEE | CMYGGVTLHDNN***RL*** | | KKEVTVQELDLQARHYL | |
| SPEA | CIYGGVTNHEGN***HL*** | | KKMVTAQELDYKVRKYL | |
| CONSENSUS | CMYGGVTLHEGN***HL*** | | KKNVTAQELD(L/Y)QAR(R/H)YL | |
| TSST-1 | IHFQISGVTNTE***KL*** | | KKQLAISTLDFEIRHQL | |

Applicants note that Table 2 in Iandolo merely lists sequences. The native toxin sequences of Table 2 are not isolated peptide sequences. No actual 12-mer peptides corresponding to those consensus sequences were made. For example, the 12-mer peptides of the claimed invention differ from the sequences in Table 2 of Iandolo by having 2 less amino acids on the C-terminal end as compared to the native sequences shown in Table 2 of the Iandolo

reference, where indicated in italics in the sequence in the table. Also, the toxin sequences from amino acids 140-163 of the Iandolo reference lack 7 amino acids at the carboxyl terminus as compared to the claimed peptide sequences of consensus region 2 of the present invention.

In fact, Iandolo simply lists "biologically active regions of proteins ...most likely to be conserved over time and should be regions of high homology" (page 389, lines 38-39). These are merely sequences and not isolated peptide sequences. Furthermore, the Iandolo reference refers to the finding that "the active site of the enterotoxins resided in the N-terminal tryptic fragment in the area immediately downstream from the C-terminal cysteine...[and that] [t]his hypothesis was based on the sequence similarities exhibited by peptides of SEA, SEB, and SEC1 derived from this region" (page 389, line 40 through page 390, line 1). Significantly, Iandolo does not disclose specific peptides, nor does this reference teach or suggest to one skilled in the art how to construct such peptides. Importantly, applicants also note that the presently claimed peptides are non-toxic and beneficial against the toxic effects of bacterial toxins. The Iandolo reference, however, presents sequences that are those of toxins themselves and thus, toxic.

Therefore, the Iandolo reference does not describe the claimed peptides, as the reference must teach every element of the claim in order to anticipate a claim according to USPTO practice and procedures. The Iandolo reference does not provide specific peptide sequences, but merely lists sequence similarities among the pyrogenic toxins and enterotoxins in Table 2.

Applicants note that claims 50-55 have been amended to include the proviso that the claimed peptide is not SEB or SEC or any other native toxin addressing the Examiner's concerns that the claimed peptides may be those sequences described in Table 2 of Iandolo. Claims 50-55 include the proviso that none of the amino acid sequences are an amino acid sequence which is found in any native toxin molecule and that the peptide is not a native toxin protein, specifically SEB or SEC which have the sequences as illustrated in Table 2 of Iandolo, more particularly, SEB: CMYGGVTEHHGNOL and $SEC_1$: CMYGGITKHEGNHF. Support for this amendment can be found, e.g., on page 24, lines 18-25 and Example 1 (page 43, lines 7-21,

first full paragraph)of the specification. The toxin sequences from amino acids 106-119 in Table 2 of the Iandolo reference have 2 additional amino acids at the carboxyl terminus as compared to the claimed peptide sequences of consensus region 1 of the present application.

Furthermore, Iandolo fails to disclose, teach, or suggest the unexpected properties of the peptide having the claimed sequences. Iandolo does not teach that a peptide having the claimed sequences inhibits binding of toxins to the MHC complex. In fact, the Iandolo reference merely presents a background of the various enterotoxins and Table 2 shows sequence similarity among the enterotoxins. Iandolo also does not teach or suggest that a peptide having the claimed sequence inhibits stimulation of blastogenesis by toxins and inhibits the toxic effects of a native toxin *in vivo*. Therefore, applicants respectfully request reconsideration and withdrawal of this §102(b) rejection in view of the aforementioned arguments.

Although the claims have not been rejected under 35 U.S.C. §103(a), applicants point out that Iandolo fails to disclose, teach, or suggest the unexpected properties of the peptide having the claimed sequences. Iandolo does not teach that a peptide having the claimed sequences inhibits binding of toxins to the MHC complex. In fact, the Iandolo reference merely presents a background of the various enterotoxins and Table 2 shows sequence similarity among the enterotoxins. Iandolo also does not teach or suggest that a peptide having the claimed sequence inhibits stimulation of blastogenesis by toxins and inhibits the toxic effects of a native toxin *in vivo*.

## CONCLUSION

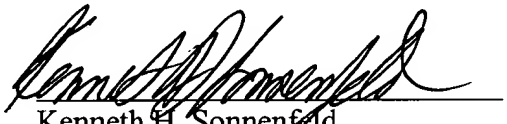
Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4010US2.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2016-4010US2. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
Morgan & Finnegan, L.L.P.

Dated: July 31, 2002

By 
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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the application as follows:

### IN THE CLAIMS

50. (Twice amended) A non-toxic, purified peptide consisting essentially of an amino acid sequence selected from the group consisting of

CMYGGVTLHDGN (SEQUENCE ID NO: 32);
CMYGGVTLHNGN (SEQUENCE ID NO: 33);
CMYGGVTLHEGN (SEQUENCE ID NO: 34);
CMYGGVTLHQGN (SEQUENCE ID NO: 35);
CMYGGVTLHHGN (SEQUENCE ID NO: 36);
CMYGGVTEHDGN (SEQUENCE ID NO: 37);
CMYGGVTEHNGN (SEQUENCE ID NO: 38);
[CMYGGVTEHEGN (SEQUENCE ID NO: 3);]
CMYGGVTEHQGN (SEQUENCE ID NO: 39);
CMYGGVTEHHGN (SEQUENCE ID NO: 40);
CMYGGVTKHDGN (SEQUENCE ID NO: 41);
CMYGGVTKHNGN (SEQUENCE ID NO: 42);
CMYGGVTKHEGN (SEQUENCE ID NO: 43);
CMYGGVTKHQGN (SEQUENCE ID NO: 44);
CMYGGVTKHHGN (SEQUENCE ID NO: 45);
CMYGGVTPHDGN (SEQUENCE ID NO: 46);
CMYGGVTPHNGN (SEQUENCE ID NO: 47);
CMYGGVTPHEGN (SEQUENCE ID NO: 48);
CMYGGVTPHQGN (SEQUENCE ID NO: 49);
CMYGGVTPHHGN (SEQUENCE ID NO: 50);

CMYGGVTNHDGN (SEQUENCE ID NO: 51);
CMYGGVTNHNGN (SEQUENCE ID NO: 52);
CMYGGVTNHEGN (SEQUENCE ID NO: 53);
CMYGGVTNHQGN (SEQUENCE ID NO: 54);
CMYGGVTNHHGN (SEQUENCE ID NO: 55);
CMYGGITLHDGN (SEQUENCE ID NO: 56);
CMYGGITLHNGN (SEQUENCE ID NO: 57);
CMYGGITLHEGN (SEQUENCE ID NO: 58);
CMYGGITLHQGN (SEQUENCE ID NO: 59);
CMYGGITLHHGN (SEQUENCE ID NO: 60);
CMYGGITEHDGN (SEQUENCE ID NO: 61);
CMYGGITEHNGN (SEQUENCE ID NO: 62);
CMYGGITEHEGN (SEQUENCE ID NO: 63);
CMYGGITEHQGN (SEQUENCE ID NO: 64);
CMYGGITEHHGN (SEQUENCE ID NO: 65);
CMYGGITKHDGN (SEQUENCE ID NO: 66);
CMYGGITKHNGN (SEQUENCE ID NO: 67);
CMYGGITKHEGN (SEQUENCE ID NO: 68);
CMYGGITKHGGN (SEQUENCE ID NO: 69);
CMYGGITKHHGN (SEQUENCE ID NO: 70);
CMYGGITPHDGN (SEQUENCE ID NO: 71);
CMYGGITPHNGN (SEQUENCE ID NO: 72);
CMYGGITPHEGN (SEQUENCE ID NO: 73);
CMYGGITPHQGN (SEQUENCE ID NO: 74);
CMYGGITPHHGN (SEQUENCE ID NO: 75);
CMYGGITNHDGN (SEQUENCE ID NO: 76);
CMYGGITNHNGN (SEQUENCE ID NO: 77);
CMYGGITNHEGN (SEQUENCE ID NO: 78);

CMYGGITNHQGN (SEQUENCE ID NO: 79); and

CMYGGITNHHGN (SEQUENCE ID NO: 80), with the proviso that the peptide is not *Staphylococcal enterotoxin* B (SEB) or *Staphylococcal enterotoxin* C (SEC) or other native toxin.

51. (Twice Amended) [A] The non-toxic, purified peptide [of] according to claim 50 wherein said amino acid sequence is selected from the group consisting of

CMYGGVTLHDGN (SEQUENCE ID NO: 32);

CMYGGVTLHNGN (SEQUENCE ID NO: 33);

CMYGGVTLHEGN (SEQUENCE ID NO: 34);

CMYGGVTLHQGN (SEQUENCE ID NO: 35);

CMYGGVTLHHGN (SEQUENCE ID NO: 36);

CMYGGVTEHDGN (SEQUENCE ID NO: 37);

CMYGGVTEHNGN (SEQUENCE ID NO: 38);

[CMYGGVTEHEGN (SEQUENCE ID NO: 3);]

CMYGGVTEHQGN (SEQUENCE ID NO: 39);

CMYGGVTEHHGN (SEQUENCE ID NO: 40);

CMYGGVTKHDGN (SEQUENCE ID NO: 41);

CMYGGVTKHNGN (SEQUENCE ID NO: 42);

CMYGGVTKHEGN (SEQUENCE ID NO: 43);

CMYGGVTKHQGN (SEQUENCE ID NO: 44);

CMYGGVTKHHGN (SEQUENCE ID NO: 45);

CMYGGVTPHDGN (SEQUENCE ID NO: 46);

CMYGGVTPHNGN (SEQUENCE ID NO: 47);

CMYGGVTPHEGN (SEQUENCE ID NO: 48);

CMYGGVTPHQGN (SEQUENCE ID NO: 49);

CMYGGVTPHHGN (SEQUENCE ID NO: 50);

CMYGGVTNHDGN (SEQUENCE ID NO: 51);

CMYGGVTNHNGN (SEQUENCE ID NO: 52);
CMYGGVTNHEGN (SEQUENCE ID NO: 53);
CMYGGVTNHQGN (SEQUENCE ID NO: 54); and
CMYGGVTNHHGN (SEQUENCE ID NO: 55).

52. (Twice Amended) [A] The non-toxic, purified peptide [of] according to claim 50 wherein said amino acid sequence is selected from the group consisting of

CMYGGVTLHDGN (SEQUENCE ID NO: 32);
CMYGGVTLHNGN (SEQUENCE ID NO: 33);
CMYGGVTLHEGN (SEQUENCE ID NO: 34);
CMYGGVTLHQGN (SEQUENCE ID NO: 35);
CMYGGVTLHHGN (SEQUENCE ID NO: 36);
CMYGGVTEHDGN (SEQUENCE ID NO: 37);
CMYGGVTEHNGN (SEQUENCE ID NO: 38);
[CMYGGVTEHEGN (SEQUENCE ID NO: 3);]
CMYGGVTEHQGN (SEQUENCE ID NO: 39);
CMYGGVTEHHGN (SEQUENCE ID NO: 40);
CMYGGITLHDGN (SEQUENCE ID NO: 56);
CMYGGITLHNGN (SEQUENCE ID NO: 57);
CMYGGITLHEGN (SEQUENCE ID NO: 58);
CMYGGITLHQGN (SEQUENCE ID NO: 59);
CMYGGITLHHGN (SEQUENCE ID NO: 60);
CMYGGITEHDGN (SEQUENCE ID NO: 61);
CMYGGITEHNGN (SEQUENCE ID NO: 62);
CMYGGITEHEGN (SEQUENCE ID NO: 63);
CMYGGITEHQGN (SEQUENCE ID NO: 64); and
CMYGGITEHHGN (SEQUENCE ID NO: 65.

53. (Twice Amended) [A] The non-toxic, purified peptide [of] according to claim 50 wherein said amino acid sequence is selected from the group consisting of

CMYGGVTLHEGN (SEQUENCE ID NO: 34)
[CMYGGVTEHEGN (SEQUENCE ID NO: 3);]
CMYGGVTKHEGN (SEQUENCE ID NO: 43);
CMYGGVTPHEGN (SEQUENCE ID NO: 48);
CMYGGVTNHEGN (SEQUENCE ID NO: 53);
CMYGGITLHEGN (SEQUENCE ID NO: 58);
CMYGGITEHEGN (SEQUENCE ID NO: 63);
CMYGGITKHEGN (SEQUENCE ID NO: 68);
CMYGGITPHEGN (SEQUENCE ID NO: 73); and
CMYGGITNHEGN (SEQUENCE ID NO: 78).

54. (Twice Amended) A non-toxic, purified peptide consisting essentially of [an] amino acid sequence [selected from the group consisting of] CMYGGVTLHEGN (SEQUENCE ID NO: 34) [and CMYGGVTEHEGN (SEQUENCE ID NO: 3)].

55. (Twice Amended) [A] The non-toxic, purified peptide of any one [of] according to claims 50 to 54 wherein said amino acid sequence is a component of a larger molecule which is retained after dialysis to remove molecules with molecular weights of less than 6000-8000 daltons with the proviso that the larger molecule is not *Staphylococcal enterotoxin B* (SEB) or *Staphylococcal enterotoxin C* (SEC) [SEB or SEC] or other native toxin.